REMARKS/ARGUMENTS

Solely in order to expedite allowance of the instant application, Applicants have cancelled the broader claims and limited the pending claims to preferred embodiments – i.e., 1) the treatment of organ or tissue transplant rejection or the treatment of graft-versus-host disease; and 2) PKC beta inhibitors selected from 3-(1-methyl-1H-indol-3-yl)-4-[1-{(1-pyridin-2-ylmethyl)-piperidin-4-yl}-1H-indol-3-yl]-pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, and a pharmaceutically acceptable salt, hydrate or solvate thereof.

Support for these amendments may be found throughout the specification, e.g., in originally pending claims 3 and 5.

Support for new claim 15 may be found, e.g., in original claim 10.

35 U.S.C. §102(b) rejection

The Examiner has maintained the 35 U.S.C. §102(b) rejection of previously pending claims 1, 3-8, and 13, arguing that Heath et al. also teach autoimmune disease other than diabetes mellitus, e.g., psoriaisis. As amended, pending claims 5 and 15 are directed to the treatment of organ or tissue transplant rejection or the treatment of graft-versus-host disease. Heath does not disclose the treatment of such disorders/disease states with the compounds disclosed therein. Accordingly, Applicants submit that Heath is not anticipatory of claims 5 and 15, and respectfully request withdrawal of this novelty-based rejection under 35 U.S.C. §102(b).

35 U.S.C. §103(a) rejection

The Examiner has maintained the 35 U.S.C. §103(a) rejection of previously pending claims 1-10 and 12-14 as unpatentable over Heath (as applied to claims 1, 3-8, and 13), further in view of Albert. The Examiner acknowledges that the PKC inhibitors of Heath are different from those of Albert, but alleges that these compounds are equivalent insofar as they are both PKC inhibitors and are known to be useful for the same purpose. For the following reasons, those rejections are respectfully traversed.

As amended, pending claims 5 and 15 are directed to the treatment of organ or tissue transplant rejection or the treatment of graft-versus-host disease using an agent selected from 3-(1-methyl-1H-indol-3-yl)-4-[1-{(1-pyridin-2-ylmethyl)-piperidin-4-yl}-1H-indol-3-yl]-pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, and a pharmaceutically acceptable salt, hydrate or solvate thereof.

Applicants respectfully submit that the Examiner has not established a prima facie case of obviousness because there is no motivation to choose the components from Heath and Albert that are necessary to achieve Applicants' methods.

A proper obviousness analysis involves a three-step analysis under *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). *Graham* requires that to make out a case of obviousness, one must:

(A) determine the scope and contents of the prior art;
(B) ascertain the differences between the prior art and the claims in issue;
(C) determine the level of ordinary skill in the pertinent art; and
(D) evaluate any evidence of secondary considerations.

MPEP § 2144.08 states that "[t]he fact that a claimed species or subgenus is encompassed by a prior art genus in not sufficient by itself to establish a prima facie case of obviousness." Rather in such a situation, an examiner must show some suggestion or motivation from the reference itself, or from the field in general, to make the claimed invention. According to MPEP §2144.08, in a genus-species situation, in light of findings made relating to the three *Graham* factors, an examiner should determine whether there is motivation to select a species from a prior aft genus by considering:

a) the size of the alleged prior art genus;

b) any teaching in the prior art to select a particular species (or subgenus) from a cited genus;

c) any teaching of structural similarity between a species or subgenus within a cited genus and the particular species (or subgenus) at issue;

d) any similar properties or uses of a structurally similar species or subgenus within the cited genus and the particular species (or subgenus) at issue;

e) any other relevant teachings supporting the selection of the particular species or subgenus at issue from the cited genus.

For the instant claims there are at least two genera from the cited art that one must address for an obviousness determination: 1) the compounds used;[1] and 2) the disorders

[1] Allegedly provided by Heath.

treated.[2] Moreover, for a proper obviousness analysis, one must consider what the cited art explicitly states or inherently implies about these genera.

Heath teaches a large genus of PKC inhibitors. (See Heath, Column 2, lines 47 – column 5, line 23). Heath teaches that the compounds therein are highly selective inhibitors of the PKC beta 1 and PKC beta 2 isozymes (see, e.g., Heath, Column 2, lines 28-34). Heath states that that "[o]nly one or two of the protein kinase C isozymes may be involved in a given disease state. For example, the elevated blood glucose levels found in diabetes leading to an isozyme-specific elevation of the beta-2 isozyme in vascular tissues." (Heath, Column 1, lines 45-49). Heath indicates that because of the isozyme selectivity of the disclosed compounds, such compounds are useful in treating disease states associated with an elevation of the beta-1 and beta-2 isozymes. (Heath, Column 2, lines 33-38). Accordingly, Heath teaches that only certain PKC isozymes are associated with certain disorders, which indicates that inhibition of a non-associated PKC isozyme would be ineffective to treat those disorders.

Albert discloses a large genus of PKC inhibitors. (See Albert at [0001]-[0040]). This genus of PKC inhibitors regulates a broad genus of PKC isozymes. (See, e.g., Albert at [0224]-[0236], disclosing regulation of PKC θ, PKC α, PKC β1, PKC δ, PKC ε, and PKC η). Albert also discloses the use of the genus of PKC inhibitors therein to treat a very large genus of disorders. For example, Albert claims that the PKC inhibitors therein are

> useful in the treatment and/or prevention of diseases or disorders mediated by T lymphocytes and/or PKC, e.g. acute or chronic rejection of organ or tissue allo- or xenografts, atherosclerosis, vascular occlusion due to vacular injury such as angioplasty, restenosis, hypertension, heart failure, chronic obstructive pulmonary disease, CNS diseases such as Alzheimer disease or amyotrophic lateral sclerosis, cancer, infectious diseases such as AIDS, septic shock or adult respiratory distress syndrome, ischemia/reperfusion injury e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, or traumatic shock. The compounds of formula I are also useful in the treatment and/or prevention of T-cell mediated acute or chronic inflammatory diseases or disorders or autoimmune diseases e.g. rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Hashimoto's thyroidis, multiple sclerosis, myasthenia gravis, diabetes type I or II and the disorders associated therewith, respiratory diseases such as asthma or

[2] Allegedly provided by Albert.

inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, cutaneous manifestations of immunologically-mediated disorders or illnesses, inflammatory and hyperproliferative skin diseases (such as psoriasis, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis), inflammatory eye diseases, e.g. Sjoegren's syndrome, keratoconjunctivitis or uveitis, inflammatory bowel disease, Crohn's disease or ulcerative colitis.

However, Albert does not indicate which PKC isozymes are associated with the disorders in the large list of those allegedly treatable by the compounds therein.

Heath clearly teaches that "[o]nly one or two of the protein kinase C isozymes may be involved in a given disease state". The compounds of Heath are PKC beta isozyme specific, and without some indication that organ or tissue transplant rejection or graft-versus-host disease would benefit from such specificity, one of skill in the art, upon reading Heath, simply would not use a compound of Heath to treat the genus of disorders of Albert.

Albert shows data at [0244] that suggests that the compound of Example 100 is useful for promoting graft survival. However, according to [0228], the compound of Example 100 is a PKC alpha inhibitor. Because Heath emphasizes that only one or two PKC isozymes may be involved in a given disease state, Albert actually teaches away from using the selective PKC beta inhibitors of Heath to treat organ or tissue transplant rejection or graft-versus-host disease. Accordingly, Albert would not lead one of skill in the art to select a PKC beta 1 or 2 inhibitor for treating organ or tissue transplant rejection, and Albert certainly would not lead one of skill in the art to select 3-(1-methyl-1H-indol-3-yl)-4-[1-{(1-pyridin-2-ylmethyl)-piperidin-4-yl}-1H-indol-3-yl]-pyrrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or a pharmaceutically acceptable salt, hydrate or solvate thereof to treat organ or tissue transplant rejection or graft-versus-host disease.

In sum, the large list of disorders in Albert is not correlated with specific PKC isozymes such that one of skill in the art would know which PKC inhibitory compound to employ in order to achieve a desired effect. In Albert's examples, only a PKC alpha inhibitor is shown to be useful in promoting graft survival. However, Heath teaches a broad genus of selective inhibitors of PKC beta 1 and beta 2, and suggests that selective inhibitors are desirable because only certain PKC isozymes are associated with certain disorders. Accordingly, there is no reason that one of skill in the art would select a Heath compound to treat organ or tissue transplant rejection or graft-versus-host disease.

CONCLUSION

In view of the foregoing distinctions and remarks, Applicants submit that the presently claimed invention is neither disclosed nor suggested by the cited references, and that all the criteria of 35 U.S.C. §112 are satisfied for the instant application. Accordingly, favorable reconsideration of the application is earnestly solicited. Please send any further correspondence relating to this application to the undersigned attorney at the address below.

Respectfully submitted,

Leslie Fischer
Attorney for Applicants
Reg. No. 58,393

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 104
East Hanover, NJ 07936-1080
(862) 778-9308

Date: September 9, 2008